IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Mundy *et al.*	Art Unit	: 1644
Serial No.	: 10/086,217	Examiner	: Maher M. Haddad
Filed	: February 21, 2002	Conf. No.	: 5114
Title	: METHODS OF TREATING MULTIPLE MYELOMA AND MYELOMA-INDUCED BONE RESORPTION USING INTEGRIN ANTAGONISTS		

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DECLARATION OF DR. GREGORY R. MUNDY UNDER 37 C.F.R. §1.132

I, Gregory R. Mundy, a citizen of U.S.A., residing in Nashville, Tennessee, hereby declare as follows:

1. I am the Director of the Vanderbilt Center for Bone Biology; a Professor of Medicine, Pharmacology, Orthopedics, and Cancer Biology; and the John A. Oates Chair in Translational Medicine at Vanderbilt University in Nashville, Tennessee. I received my initial doctoral degree in Medicine and Surgery from the University of Melbourne in Australia and my second degree in Medicine from the University of Tasmania in Australia, and I did postdoctoral work at the University of Rochester in New York. I have over 35 years experience in the field of bone disease. I have published over 540 scientific articles, including 2 articles specifically on integrin studies. A copy of my CV is attached.

2. I have reviewed the above-referenced patent application and the references discussed herein.

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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3. I have been advised and understand that the Examiner has rejected claims 86-89, 91, 93-97, and 101, which are directed to methods of treating multiple myeloma with an anti-I4 integrin antibody and a chemotherapeutic agent, as being unpatentable over Van Zaanen *et al.*, *Br. J. Haematol.* 102:783-790, 1998 ("Van Zaanen") in view of Masellis-Smith *et al.*, *Cancer Res.* 57:930-936, 1997 ("Masellis-Smith") and Lokhorst *et al.*, *Blood* 84:2269-2277, 1994 ("Lokhorst") and U.S. Patent No. 5,885,786 (1996) ("Cabot") or Alexanian *et al.*, *J. Am. Med. Assoc.* 208:1580-2685, 1969 ("Alexanian"). The Examiner argues that, at the time of priority (September 13, 1999), one of ordinary skill in the art would have been motivated to substitute anti-I4 antibodies for the anti-IL-6 antibodies taught by Van Zaanen, and to further combine the anti-α4 antibody with the chemotherapeutic agent melphalan, as taught by Cabot and Alexanian, for the treatment of multiple myeloma (MM).

4. At the time of filing, a practitioner of ordinary skill in this field would not, for numerous reasons, have believed that anti-α4 antibodies, such as anti-VLA-4 antibodies, would be interchangeable with anti-IL-6 antibodies to treat MM. First, the art did not teach the anti-IL-6 antibodies could be used to treat MM. For example, Bataille *et al.* ("Biological Effects of Anti-Interleukin-6 Murine Monoclonal Antibody in Advanced Multiple Myeloma" *Blood* 86:685-691, 1995; cited in the IDS submitted June 21, 2002; courtesy copied enclosed as Exhibit A) taught that anti-IL6 antibodies were not effective at treating MM. Bataille *et al.* reported that patients with advanced MM did not achieve remission or improved outcome following treatment with murine anti-IL6 monoclonal antibodies. Van Zaanen, which is relied upon by the Examiner, is a phase I dose-escalating study that, at best, shows that anti-IL-6 antibodies are not toxic. None of the patients involved in the study achieved a response according to standard criteria, even though effective IL-6 blocking was detected in 11/12 patients. See Van Zaanen in the abstract and in the discussion at page 787. The teachings of Van Zaanen do not overcome or refute the prior teachings of Bataille *et al.* that anti-IL-6 antibodies are ineffective for the treatment of MM. Evidence that anti-VLA-4 antibodies decreased tumor burden *in vivo* in a mouse model of myeloma bone disease is presented in the

above-referenced application (see, *e.g.*, page 66, lines 14-26), and the results of these studies were published in Mori *et al.* ("Anti-α4 integrin antibody suppresses the development of multiple myeloma and associated osteoclastic osteolysis," *Blood* 104:2149-2154, 2004, cited in the information disclosure statement (IDS) submitted herewith).

5. The Examiner has cited Lokhorst *et al.* as evidence that anti-VLA-4 antibodies inhibited IL-6 secretion *in vitro* by long term bone marrow cultures (LTBMCs) contacted with MM cells. The Examiner has considered this evidence in combination with Van Zaanen and Masellis-Smith to conclude that anti-VLA-4 antibodies can be used for the treatment of MM. One of ordinary skill in this field, however, would not arrive at this conclusion. In view of the fact that anti-VLA-4 antibodies decrease tumor burden in mouse models of myeloma bone disease, and that anti-IL-6 is not effective as a treatment for myeloma[1] (see paragraph 4), one of ordinary skill in this field would conclude that although anti-VLA4 antibodies can decrease IL-6 levels (at least *in vitro*), this does not appear to be relevant to the anti-tumor effect of the anti-VLA-4 antibodies. Anti-VLA-4 antibodies are believed to work through mechanisms that are independent of IL-6. Anti-VLA-4 antibodies kill myeloma cells by blocking direct interactions between myeloma cells and normal host cells in the bone marrow. When the myeloma cells cannot attach to the normal host cells, the myeloma cells die. There may be a concomitant decrease in IL-6 levels following administration of anti-VLA-4, but this is a byproduct and not the direct cause of myeloma cell death, nor the reason why the myeloma cells die.

6. At the time of filing, a practitioner of ordinary skill in this field would not have believed that anti-VLA-4 antibodies could substitute for the prednisone taught by Alexanian *et al.* in a combination therapy with melphalan for the treatment of MM. One of ordinary skill in the art would not make this substitution at least because anti-VLA4 antibodies and prednisone

[1] Bataille *et al.* report that some MM patients experienced improvements in some symptoms following treatment with a murine anti-IL-6 monoclonal antibody. For example, of the 3 patients who succumbed to progressive MM after less than 1 week of treatment, 2 exhibited marked inhibition of plasmablastic proliferation. Of the seven remaining patients, 3 had objective antiproliferative effect marked by a significant reduction of the myeloma cell labeling index within the bone marrow. One of these 3 patients received a 30% regression of tumor mass. The authors concluded, however, that none of the patients studied achieved remission or improved outcome as judged by standard clinical criteria. See Bataille *et al.* in the abstract.

are different types of molecules having different therapeutic targets, and therefore different therapeutic effects. As described in paragraph 5, anti-VLA4 antibodies are very specific targeting molecules that kill myeloma cells by blocking direct interactions between myeloma cells and normal host cells in the bone marrow. Prednisone is a broad spectrum agent which kills cancer cells regardless of whether or not they are interacting with other cells. Thus whether prednisone and melphalan in combination can be used to treat MM (as described in Alexanian) is irrelevant insofar as predicting whether a combination of an anti-VLA-4 antibody and melphalan can be used to treat MM. Even in view of Van Zaanen, Masellis-Smith, and Lokhorst, a therapeutic effect of a combination therapy of prednisone and melphalan for treatment of MM is not predictive of a therapeutic effect of a combination therapy of anti-VLA-4 antibodies and melphalan.

7. Evidence that an anti-IL6 receptor antibody in combination with melphalan can treat MM, as described in Nakamura (U.S. Patent No. 6,692,742) is also irrelevant insofar as predicting whether a combination of an anti-VLA-4 antibody and melphalan can be used to treat MM. An anti-IL6 receptor antibody will disrupt a multitude of pathways, as this receptor interacts with a class of ligands called gp130 ligands and gp80 ligands. See, *e.g.*, Schwabe *et al., J. Biol. Chem.* 269:7201-7209, 1994, cited on the attached IDS. Thus in view of evidence that a combination of anti-IL-6 receptor antibodies and melphalan can treat MM, one of skill in the art would not conclude that an anti-VLA-4 antibody (which disrupts a very different interaction) in combination with a chemotherapeutic agent would also be effective for the treatment of MM. As described in paragraph 5, studies described in the prior art indicate that anti-VLA-4 antibodies kill myeloma cells through a mechanism that is independent of IL-6.

8. A combination of melphalan and anti-VLA-4 antibody was observed to have a synergistic effect on the treatment of MM (see the specification at page 72, lines 6-20). As shown in Figure 8 of the specification, treatment with antibody alone (200 µg initial dose for the first week, followed by a maintenance dose of 100 µg) reduced IgG2b levels from about 2.7 mg/mL to about 2 mg/mL, and treatment with melphalan alone (100 µg) similarly reduced IgG2b levels from about 2.7 mg/mL to about 2 mg/mL. However, treatment with the

combination of antibodies and melphalan resulted in a much more significant decrease in IgG2b levels (from about 2.7 mg/mL to about 0.3 mg/mL). The effect of IgG2b levels is indicative of a decrease in tumor burden. The synergistic result observed with the combination of melphalan and anti-VLA-4 was unexpected and surprising because there was no reason to expect such a dramatic improvement in view of the mild effects observed with either melphalan or antibody alone.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

DATE: Sept 11, 2006

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